REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. No claims have been amended. Therefore claims 26-48 are pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as lacking in written description.

Applicant has stated previously that the specification describes both structure (an oligonucleotide with at least one phosphorothioate bond) and structure/function correlation (an oligonucleotide with at least one phosphorothioate bond induces an immune response). The Examiner states that McIntyre et al. supports the assertion that "not all oligonucleotides elicit an immune response" and that the specification "does not provide support as to the necessary structure of the oligonucleotide to stimulate an immune response." Applicant has previously respectfully disagreed with this broad interpretation of McIntyre (see Applicant's remarks in the amendment dated July 25, 2006, page 6, paragraph 2). McIntyre teaches only one nucleotide, for which the data were interpreted as indicating a sequence-specific immune effect. However McIntyre later proposes other possible explanations for the data (McIntyre, p318). Therefore, McIntyre does not broadly teach that phosphorothioate oligonucleotides do not elicit non-specific effects or immune responses. In addition, the claimed invention is limited to a cell-mediated immune response. As the teachings of McIntyre are directed to a humoral immune response these teachings are therefore not directly applicable to claims directed to a cell-mediated immune response.

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as lacking enablement.

The test of enablement is whether undue or unreasonable experimentation is required for one of ordinary skill in the art to practice (i.e., make and use) the claimed invention. Thus, based on the specification and the knowledge in the art at the time of filing (i.e., effective filing date), one of ordinary skill must be able to make and use the claimed invention without undue experimentation.

The experimentation may be complex and still not undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive of the issue of enablement.

Nature of the invention and breadth of the claims: The invention relates in part to the use of phosphorothioate oligonucleotide analogs as immunopotentiators to stimulate a cell-mediated immune response. The claims relate to administering a phosphorothioate oligonucleotide analog by a route selected from the group consisting of inhalation, opthamalic, intranasal, parenteral, oral and intradermal to a human as an immunopotentiator.

Level of ordinary skill in the art: The level of ordinary skill in the art is high. Ordinary artisans would include medical practitioners who treat cancer, infectious disease, and patients undergoing surgery using any of a number of treatment modalities known in the art at the time of filing. A high level of ordinary skill in the art lessens the amount of direction to be provided by the inventor(s) since one of ordinary skill will be accustomed to the experimentation required to practice the claimed invention.

State of the art and level of predictability in the art: The Examiner cites Crooke (Bio/technology 1992 Vol. 10 No. 8 pages 882-886) as teaching that the "activity of ISIS 1082 [is] equivalent to trifluorothymidine in cornea of mice, but less active in other animal models" to support her argument that Applicant has not enabled the claimed genus. However, Crooke et al. does not make clear whether ISIS 1082 is being compared to trifluorothymidine in other mouse models or used alone, what the other mouse models are (such as whether they are models of a condition for which immunostimulatory phosphorothioate oligonucleotide analogs would be useful for treatment), or whether the method of administration was topical application to the cornea as in Crooke or some other method of administration. Therefore, the teachings of Crooke do not give clear support to the assertion that the practice of the claimed methods is unpredictable.

Amount of direction provided by the inventor: Applicant has provided sufficient guidance to allow one of skill in the art to practice the claimed invention. The manufacture and administration of oligonucleotide drugs was known in the art at the time of filing. The instant specification on page 9, lines 19-25 states that "oligonucleotide drugs have been safely administered to humans and several clinical trials of antisense oligonucleotide analog drugs are presently underway. It is, thus, established that oligonucleotides and analogs can be useful therapeutic instrumentalities and that the same can be configured to be useful in regimes for treatment of cells, tissues and animals, especially humans."

The Examiner asserts that a "molecule inducing an immune stimulus against a viral infection would not necessarily induce an immune stimulus effective against a cancer cell. The claimed phosphorothioate oligonucleotide analogs are described as immunopotentiators. Page 10 line 36 – page 11 line 7 of the specification states that "[i]n the context of this invention, the term "immunopotentiator" refers to a material which produces non-specific immune stimulation. Immune stimulation can be assayed by measuring various immune parameters, for example antibody-forming capacity, number of lymphocyte subpopulations, mixed leukocyte response assay or lymphocyte proliferation assay. Immune stimulation may result in increased resistance to infection or resistance to tumor growth upon administration." Therefore, administration of the phosphorothioate oligonucleotide analogs results in a general immune stimulus that is useful for treating conditions that respond to an elevated immune response such as cancer or infectious disease. Furthermore, the specification provides guidance for the administration of the phosphorothioate oligonucleotide analogs (see pages 13-14 of the specification).

Therefore, administration of phosphorothioate oligonucleotide analogs to stimulate an immune response in a human would be possible without undue experimentation using methods known in the art.

Working examples: The Examiner has stated that the "specification discloses the phosphorothioate molecules to be antisense or complementary to viral RNAs; thus the oligos used in the examples cannot be not-antisense as claimed". The Examiner cites Branda (Biochemical Pharmacology (1993) Vol. 45 No. 10, pages 2037-2043), which teaches antisense molecules, as being the closest prior art. While the instant specification discloses phosphorothioate

oligonucleotide analogs that are antisense molecules, it also teaches that these molecules have a second property, sequence non-specific immune stimulatory capacity. Page 8, lines 23-28 of the instant specification teach that it has "been found that oligonucleotide analogs having at least one phosphorothioate bond can be used to induce stimulation of a systemic or humoral immune response. Thus, these oligonucleotides are also useful as immunopotentiators of an antibody response, either alone or in combination with other therapeutic modalities." The specification also discloses that "[t]his immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess." (Page 8, lines 12-15). This disclosure supports the assertion above that phosphorothioate oligonucleotide analogs with at least one phosphorothioate bond stimulate an immune response in general, whether or not they are antisense oligonucleotides. The data demonstrate the oligonucleotide is working through a mechanism that is independent of an antisense mechanism. While the working examples in the instant specification disclose phosphorothioate oligonucleotide analogs that are antisense, the courts have previously held that a specification need not contain a working example (e.g. of a phosphorothioate oligonucleotide analog that is not antisense) if the disclosure of the invention is adequate to allow one of ordinary skill to practice it without undue experimentation (i.e., if the disclosure is otherwise enabling). In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). As argued above, the instant disclosure meets this requirement.

In view of the totality of the factors discussed above, the lack of a working example directed toward phosphorothioate oligonucleotide analogs that are not antisense, does not preclude enablement of the present invention, particularly when the data has demonstrated a mechanism of action that is not related to it's antisense features.

Quantity of experimentation: The quantity of experimentation needed to make and use the invention, in view of the disclosure and the state of the art at the time of filing, is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Double Patenting Rejection

The Examiner rejected claims 26, 28, 29, and 30 as being unpatentable over claims 1-8 of U.S. Patent No. 6,727,230 (Hutcherson et al.) in view of U.S. Patent 5,356,882 (Walker et al.).

Stated again for the record, applicants may consider filing a Terminal Disclaimer if some claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

Specification Objection

The specification has been objected to as failing to provide proper antecedent basis for the claimed subject matter.

The specification describes oligonucleotide analogs having "both therapeutic efficacy (through antisense or other means) and immunopotentiating activity." As the specification gives a number of alternatives for the activity of phosphorothioate oligonucleotide analogs, including immunopotentiating activity and antisense, the specification as filed therefore provides support for the term "not antisense". Antisense oligonucleotides function by binding to a complementary RNA sequence and preventing production of a protein. The function of antisense oligonucleotides is dictated by the structure. The primary structure of an antisense oligonucleotide, the nucleotide sequence, determines whether the oligonucleotide is complementary to an RNA. The fact that applicant has taught in the specification that the oligonucleotides can work independent of an antisense method, clarifies that the invention is not limited to antisense oligonucleotides. Not all phosphorothioate containing oligonucleotides are antisense oligonucleotides. The basis of the invention is that phosphorothioate oligonucleotides are immune stimulatory even when they are not antisense oligonucleotides. Paragraph 0016 of the specification teaches "It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. *This immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess.*" emphasis added. The term cannot lack antecedent basis in the specification, when it is an important part of the discovery of the invention.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____

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